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Editorial Comment

Adjuvant chemotherapy in colon cancer – Is it worth it?

*Axel Grothey**

Mayo Clinic Rochester, 200 First Street SW, Rochester, MN 55905, USA

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Two decades since the first demonstration that 5-fluorouracil (5-FU)-based adjuvant chemotherapy improves survival in resected colon cancer,[1] the standard of care of adjuvant chemotherapy in this disease has been shaped by several pivotal phase III trials and meta-analyses.[2,3] Adjuvant treatment still relies on a fluoropyrimidine backbone (5-FU/FA (folinic acid) or capecitabine) with the addition of oxaliplatin for stage III colon cancers and select stage II cancers to form the FOLFOX, XELOX, or – less utilised – the FLOX regimen. More recent data question the use of oxaliplatin in elderly patients over the age of 70, and so far no survival benefit has been established with oxaliplatin for patients with stage II disease, although patients with clinically 'high-risk' stage II cancers experience a longer disease-free survival when treated with FOLFOX compared with 5-FU/FA alone.[4,5] The drugs used in the adjuvant treatment will likely not change over the next 5–10 years since 3 of 4 tested agents, irinotecan, cetuximab and bevacizumab, which all demonstrated activity in advanced colorectal cancer failed to provide significant benefit in phase III adjuvant trials.

The goal of adjuvant therapy is primarily to increase cure rates in resectable colon cancer, but in order to perform a true value assessment, one has to take a more comprehensive approach and include the following parameters: efficacy of therapy (potential gain in lifetime, probability of cure), toxicity/lethality, financial costs, convenience and ease of administration of therapy and patient preference.

This last point, patient preference, is highlighted in the article by Blinman et al. in this issue of the European Journal of Cancer.[6] The study surveyed 123 patients with resected colon cancer who had completed adjuvant chemotherapy to determine for which hypothetical survival benefit derived from their therapy they considered the adjuvant treatment worthwhile. The study comprised interviews and questionnaires and used a time trade-off method to determine the minimal survival benefit that patients judged to be sufficient to make adjuvant chemotherapy worthwhile and based on their experiences as to how good or bad it was. Interestingly, the majority of patients considered even small potential survival benefits worthwhile. These findings are in line with prior observations in other cancers in adjuvant scenarios and mirror results recently presented from a similar survey in American patients with colon cancer.[7,8] However, in the present study a small proportion of patients who judged even the largest possible survival benefit of 15 years, not sufficient to make chemotherapy worthwhile. This variability is unexpected, but could also

* Tel.: +1 507 284 2779; fax: +1 507 284 1803.
E-mail address: grothey.axel@mayo.edu
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be due to inherent problems with the way the survey was conducted. About 50% of patients included in the analysis considered an improvement of 1 (one) day in overall survival enough to justify their decision for adjuvant therapy. This almost certainly confirms the presence of 'cognitive dissonance reduction', as nicely laid out by the authors themselves. It appears to be inherent to humans to retrospectively justify personal decisions by almost any means. This inherent bias of the analysis makes an interpretation of the results difficult. One would like to see a patient cohort interviewed before adjuvant therapy, and even better, before and after adjuvant therapy. In addition, the time range allowed to qualify for the study after completion of chemotherapy (3–60 months) was quite wide and almost certainly introduced some recall bias. In a larger cohort, one could look for time-related trends, but the small sample size of the survey precluded a more detailed analysis here. Another critical factor of the study is the low percentage of patients treated with the current standard of care, which – at least for stage III colon cancer – is an oxaliplatin-based regimen. Although the statistical analysis in this survey did not demonstrate any difference in preference between patients with and without oxaliplatin-based therapy, the small number of patients receiving oxaliplatin (and presumably, most of them were treated with FLOX and not FOLFOX) makes the analysis difficult to interpret for our current standard of care.

Returning to the concept of 'value of adjuvant chemotherapy', one of the key issues is that the majority of patients will not benefit from treatment. In stage III colon cancer 40–50% of patients are cured by surgery alone, and almost 35% relapse anyway, in spite of the use of FOLFOX. In stage II cancers, we are faced with an even worse benefit ratio: 60–70% of patients are cured by surgery, 15–20% relapse in spite of adjuvant therapy. The benefits of therapy with regard to overall survival are even more attenuated. In the pivotal QUASAR trial, the survival benefit associated with adjuvant 5-FU/FA for patients with stage II colon cancer was 2.7% at 5 years, meaning that more than 97% of patients received 6 months of chemotherapy unnecessarily. These data indicate the urgent need to better identify patient populations at risk of recurrence and to develop markers to predict the activity of adjuvant chemotherapy. The risk–benefit ratio, i.e. the value of adjuvant therapy could be greatly enhanced with the identification of prognostic and predictive markers. In addition, the value could be increased by a reduction in the toxicity, cost and inconvenience associated with adjuvant therapy.

Towards these ends, various commercially available molecular tests (e.g. Oncotype DX Colon, Coloprint, Previstage) have already been developed or are undergoing clinical validation which all promise to provide refined prognostic information for patients with resected colon cancer.[9–11] Unfortunately, we are still lacking reliable predictive markers for the selection of adjuvant chemotherapy.

The issue of toxicity, cost and inconvenience of adjuvant therapy, is being addressed in a large international collaboration which is currently underway to determine in a preplanned, pooled analysis of various trials if the duration of adjuvant chemotherapy can be reduced. This project, called International Duration Evaluation of Adjuvant therapy (IDEA), currently includes four adjuvant phase III trials conducted worldwide which all randomise patients to 3 versus 6 months of oxaliplatin-based therapy as part of their study design. Eventually, more than 10,500 patients with stage III colon cancer will be available for a non-inferiority analysis with clinically relevant, tight non-inferior margins.

These efforts will hopefully in the end live up to the perspective of a less-toxic, cheaper and more convenient individualised adjuvant therapy with better identification of patients at risk and utilisation of a tailored adjuvant therapy rather than a one-size-fits-all approach with very little variation in treatments.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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